REMARKS/ARGUMENTS

Reconsideration is requested. Claims 1-25 are pending.

NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

Claims 1-25 stand rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-26 of U.S. Patent 5,968,914 (the '914 patent). Applicants traverse.

> A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

35 U.S.C. 121.

The '914 patent issued from application Serial No. 08/472,210 (filed on June 7, 1995) which is a continuation-in-part of application Serial No. 08/176,485 (the '485 application). During prosecution of the '485 application, Examiner Kunz required restriction among the claims. Office Action mailed June 28, 1994 in the '485 application. He found there were three distinct inventions: Group I (claims 1-25 drawn to methods for preventing or treating the toxicity caused by pyrimidine nucleosides), Group II (claims 27-47 drawn to methods for treating cancer), and Group III (claims 75-87 drawn to compositions of acylated pyrimidine nucleosides and a chemotherapeutic agent). The claims of the '914 patent are drawn to methods for treating cancer.

This application is a divisional of the '485 application filed before the issuance of the '914 patent. The pending claims are drawn to methods for preventing or treating the

toxicity caused by pyrimidine nucleosides. Therefore, 35 U.S.C. § 121 prohibits using the '914 patent as a reference against this application.

Moreover, the restriction requirement in the parent '485 application is evidence that the pending claims 1-25 are patentable over claims 1-26 of the '914 patent because methods for preventing or treating the toxicity caused by pyrimidine nucleosides (i.e., the invention claimed in this application) are distinct from methods for treating cancer (i.e., the invention claimed in the '914 patent).

Claims 1-25 also stand rejected under the judicially-created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 48-74 of copending application Serial No. 08/473,332 (the '332 application). Applicants traverse.

The pending claims 1-25 are drawn to methods for preventing or treating the toxicity caused by pyrimidine nucleosides. Claims 48-74 of the '332 application are drawn to methods for treating viral infections. Both methods, as well as the methods of treating cancer claimed in the '914 patent, involve administering an acylated derivative of a non-methylated pyrimidine nucleoside. On pages 5-6 of the Action, the Examiner noted the difference between claims 1-25 of this application and claims 48-74 of the '332 application, but he alleged:

> [T]he scope of the instant claims includes the uses generically associated with the pyrimidine nucleoside, thus recitation of uses of the pyrimidine nucleoside as set forth in the species of either cancer or viruses would be obvious to one of skill in the art. It would have been *prima facie* obvious to use a acyl derivative of a non-methylated pyrimidine nucleoside with a pyrimidine nucleoside.

This is incorrect. As discussed above with respect to the double patenting rejection over the '914 patent, the Patent Office has established that pending claims 1-25 are

patentably distinct over methods of treating cancer. Therefore, the Examiner needs to show why pending claims 1-25 are obvious over the invention drawn to methods of treating a viral disease (i.e., claims 48-74 of the '332 application) because the alleged genus-species relationship is not sufficient to establish a case of *prima facie* obviousness. Clearly, the species of treating cancer claimed in the '914 patent and the genus claimed in this application are patentably distinct. If the Examiner does not provide evidence showing that one of ordinary skill in the art would have been motivated to modify methods for **treating a viral disease** (claims 48-74 of the '332 application) to methods for **preventing or treating toxicity caused by pyrimidine nucleosides** (claims 1-25 of this application), then this double patenting rejection cannot be maintained.

Furthermore, Applicants submit that requiring submission of a terminal disclaimer or cancellation of conflicting claims while other rejections in both application are pending is an incorrect procedure for addressing a "provisional" double patenting rejection.

> If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

M.P.E.P. § 804 I.B. at 800-19.

This is a **provisional** non-statutory obviousness-type double patenting rejection. In accordance with the above procedure, Applicants submit that the issues raised by the Section 103 rejections discussed below should be resolved first. If the Examiner is not persuaded to withdraw this double patenting rejection on substantive grounds (i.e.,

methods for preventing or treating toxicity caused by pyrimidine nucleosides are patentably distinct over methods for treating a viral disease) then, in accordance with the procedure described by M.P.E.P. § 804, the application in which only the provisional double patenting rejection remains is permitted to issue as a patent and a double patenting rejection is made in the other application when the patent issues. Terminal disclaimers will be submitted, conflicting claims will be canceled, or other action taken upon an indication that the pending claims are otherwise allowable. To require submission of a terminal disclaimer prior to an indication that the claims are otherwise allowable would constitute an undue burden on Applicants because of the cost of the terminal disclaimer fee and the uncertainty of the scope of claims allowed in this application and the '332 application.

Withdrawal of the double-patenting rejections is requested.

OBVIOUSNESS REJECTIONS

Claims 1-15, 18-19 and 22-25 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Martin et al. (*Cancer Research* 42:3964-3970, 1982) or Sommadossi et al. (*Antimicrobial Agents and Chemotherapy* 32:997-1001, 1988) when taken in view of von Borstel et al. (WO 89/03837) and Falcone et al. Applicants traverse.

The invention of the present application is directed to a method for the prevention or treatment of toxicity due to a pyrimidine nucleoside analog. The method comprises the steps of administering to an animal a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

As admitted in the Action (page 7), neither Martin et al. nor Sommadossi et al. suggested the use of acylated uridine or cytidine derivatives. In an attempt to cure this deficiency, the Examiner relies on von Borstel et al. and asserts that it would have been obvious to one of ordinary skill to have substituted acylated uridine or cytidine as described by von Borstel et al. in place of the free uridine disclosed by Martin et al. and Sommadossi et al. in order to increase serum and tissue levels of uridine and thereby reduce toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of the nucleoside analog. Applicants disagree for the following reasons.

Martin et al. (and others, e.g., Peters et al. (Brit. J. Cancer 57:259-265, 1988)) disclose the use of uridine to reduce toxicity of 5-fluorouracil. This permits 5-FU dose escalation and a consequent net improvement in antitumor efficacy.

However, Falcone et al. (discussed in more detail below) discloses that raising levels of uridine in the plasma higher than those achieved by low-dose uridine alone or BAU alone does not result in any improvement in counteracting AZT toxicity. Based on Falcone et al., therefore, one of ordinary skill would not have been motivated to embark on an approach of therapy wherein uridine plasma levels are increased.

In addition, **unexpected** results have been obtained according to the present invention when acyl derivatives of uridine of the invention, e.g., 2',3',5'-triacetyluridine (TAU), are administered orally in conjunction with 5-FU. This is discussed in the specification at pages 42-44 and Example 6. Neither Martin et al. nor Peters et al. was able to induce even partial (50%) regressions of the murine adenocarcinoma colon 26 with high-dose 5-FU alone at the maximum tolerated dose (100 mg/kg/week). In

contrast, high-dose 5-FU in combination with oral TAU consistently results in a high incidence (60-80%) of complete regressions of established tumors.

Moreover, Kralovansky et al. (Cancer Chemother. Pharmacol. 32:243-248, 1993) (further copy attached) report that uridine administration after 5FU does not reduce the severity of gastrointestinal activity due to 5FU, although it does accelerate recovery from GI damage. In contrast, in human clinical trials with oral TAU administered after high dose 5FU, there is a remarkable reduction of gastrointestinal damage indicated by the no grade 3 or grade 4 mucositis or diarrhea in patients receiving up to 100 mg/m^2 5FU per week (Kelsen et al., J. Clin. Oncol. 15:1511-1517, 1997, which was submitted with the IDS dated May 22, 2002). Such toxicities are not uncommon in patients receiving normal clinical doses (500 to 600 mg/m^2 per week) of 5FU.

Thus, acyl derivatives of pyrimidine nucleosides provide **unexpected** benefits beyond those that have been reported for parenteral or oral administration of uridine when used to modify the toxicity and efficacy of antineoplastic pyrimidine nucleoside analogs. These same unexpected benefits are observed when TAU is administered with an inhibitor or uridine phosphorylase, e.g., benzolyoxybenzylacyclouridine, but not when the uridine phosphorylase inhibitor alone is administered (M. el Kouni, unpublished results).

Von Borstel et al. describes methods of delivering acyl derivatives of uridine or cytidine for the treatment of cardiac insufficiency, myocardial infarction, cirrhosis of the liver, cerebrovascular disorders, respiratory distress syndromes and diabetes. The methodology as specifically claimed in the present application is in no way disclosed or

suggested by von Borstel et al., either when taken alone or in combination with Martin et al. and/or Sommadossi et al. and Falcone et al.

Claims 18-19 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g., AZT) comprising administering to an animal an acylated derivative of uridine, deoxyuridine or cytidine; and an inhibitor of uridine phosphorylase. As conceded on page 8 of the Action, Martin et al., Sommadossi et al. and von Borstel et al. fail to teach the use of an inhibitor of uridine nucleoside phosphorylase. The Examiner relies on Falcone et al. (Blood 76:2216-2221, 1990) as a disclosure relating to the use of an inhibitor of uridine nucleoside phosphorylase, benzylacylouridine (BAU), to increase the serum and tissue levels of free uridine, thereby reducing the toxicity of AZT. Based on Falcone et al., in combination with the Martin et al., Sommadossi et al. and von Borstel et al. publications, it is alleged that it would have been obvious to administer acylated uridine or cytidine in combination with a uridine phosphorylase inhibitor to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine. This position is respectfully traversed.

To make out *a prima facie* case of obviousness, it is not sufficient that the teaching of the prior art could have been modified to arrive at the claimed invention. Rather, the USPTO bears the burden of establishing that there was **motivation**, based on the prior art, to do so. As stated by the CAFC in *In re Vaeck*:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should... carry out the process; and (2) whether the prior art would also

> have revealed that in so... carrying out, those of ordinary skill would have a reasonable expectation of success.... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. (internal citations omitted)

In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

In looking for a motivation to combine the references, the Examiner presents two arguments based on two different allegedly beneficial effects of uridine phosphorylase inhibitors:

(a) to increase the serum and tissue levels of free uridine; and

(b) to avoid toxicity associated with the degradation of plasma uridine to uracil.

Both arguments are wrong.

(a) No Motivation to Further Increase *In Vivo* Uridine

The Examiner asserted on page 8 of the Action that the uridine elevating effects of a uridine phosphorylase inhibitor provide the motivation to combine such an inhibitor with an acylated uridine or cytidine. This is not the case.

As is clear from Falcone et al., one of ordinary skill in the art would **not** have been motivated to combine an inhibitor of uridine phosphorylase with a source of uridine in order to prevent or treat toxicity due to a pyrimidine nucleoside analog. Falcone et al. teaches that the increased *in vivo* levels of uridine resulting from such combination did not result in reductions in AZT toxicity as compared to the uridine phosphorylase inhibitor BAU alone or uridine alone. This can be seen from Falcone et al., which states:

> Indeed, our present observation that BAU doses above 300 mg/kg/d, or combinations of BAU with low doses of exogenous Urd, do not result in improved therapeutic efficacy as compared with BAU alone (300 mg/kg/d) supports previous in vitro observations that the maximum ability of

> exogenous Urd to reverse AZT cytotoxicity is achieved at the relatively low Urd concentration of 50 μmol/L.

Falcone et al. (paragraph bridging pages 2219 and 2220).

Based on the above-quoted passage from Falcone et al., one of ordinary skill in the art would **not** have expected that the combination of a uridine phosphorylase inhibitor (such as BAU) and a source of uridine would result in improved efficacy in preventing or treating toxicity due to a pyrimidine nucleoside analog compared to either the uridine phosphorylase inhibitor alone or the source of uridine alone. Falcone et al. would have led one of ordinary skill in the art to expect that high plasma levels of uridine, however achieved, are no more effective than relatively lower plasma levels of uridine in counteracting the toxic effects of a pyrimidine nucleoside analog such as AZT. One of ordinary skill in the art would not have had the reasonable expectation of success necessary to sustain a *prima facie* case of obviousness.

Falcone et al. further teaches that higher doses of exogenous nonacylated uridine (Urd) do result in higher plasma levels of uridine in a dose-responsive manner. Falcone et al. states:

> Analysis of the plasma kinetics of the various Urd doses used in these studies (Fig 3) indicates that for doses below 1,000 mg/kg the clearance was rapid (half-life approximately 20 minutes), and the plasma concentration of Urd was normal within 2 to 3 hours. In contrast, at doses above 2,000 mg/kg, plasma Urd levels remained significantly elevated (>1mmol/L) for several hours, probably reflecting a saturation of its clearance.

Falcone et al. (page 2218, left column; see also Fig. 3).

As seen from the above-quoted passage and from Figure 3 of Falcone et al., increasing the dose of exogenous nonacylated uridine resulted in increasing plasma

levels of uridine *in vivo*. Therefore, the supposed inability of nonacylated uridine to increase plasma levels of uridine is nonexistent and thus cannot be used to explain away Falcone et al. Falcone et al. teaches one of ordinary skill in the art that increased plasma levels of uridine can be achieved utilizing the combination of uridine and a uridine phosphorylase inhibitor, but that such increased levels do not result in improved efficacy in treating or preventing AZT toxicity.

(b) Falcone et al. Does Not Teach Preventing Uracil Toxicity

The Examiner has also taken the position that the ability of a uridine phosphorylase inhibitor to prevent toxicity associated with the degradation of plasma uridine to uracil provides the motivation to combine such an inhibitor with an acylated uridine or cytidine. However, Falcone et al. nowhere teaches that BAU or any other uridine phosphorylase inhibitor exerts its beneficial effects by preventing the supposedly toxic degradation of uridine to uracil. In fact, Falcone et al. says nothing about uracil toxicity. Rather, Falcone et al. teaches that BAU exerts its beneficial effect by increasing plasma levels of uridine (Urd). Falcone et al. states:

> In summary, we have demonstrated the therapeutic utility of concomitant BAU and AZT therapy in a murine retroviral model. Enhanced efficacy appears to be related to the ability of BAU to elevate the plasma concentration of Urd and thus reduce AZT-related marrow toxicity, without impeding antiretroviral activity. (underlining added)

Falcone et al. (page 2220, paragraph bridging left and right columns).

As seen from the above-quoted passage, Falcone et al. teaches that the uridine phosphorylase inhibitor BAU exerts its beneficial effect by raising plasma levels of uridine, not by avoiding any supposed toxicity associated with degradation of uridine to uracil. However, as discussed above, Falcone et al. teaches that raising levels of

uridine in the plasma higher than those achieved by low-dose uridine alone or BAU alone does not result in any improvement in counteracting AZT toxicity.

Claims 16-17 and 20-21 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Bhalla et al. (*Blood* 70:568-571, 1987) when taken in view of von Borstel et al. (WO 89/03838) and Hanze et al. (U.S. Patent 4,017,606). Applicants traverse.

As admitted in the Action (page 8), Bhalla et al. fails to describe the use of acylated deoxycytidines in place of free deoxycytidine. In an attempt to cure this deficiency, the Examiner relies on von Borstel et al. in view of the mention in that disclosure of acylated deoxycytidine. However, one of ordinary skill in the art would **not** have been motivated to arrive at the presently claimed method on the basis of the combined disclosures of Bhalla et al. and von Borstel et al., since there is no suggestion in Bhalla et al., taken alone or in combination with von Borstel et al., of the methodology as claimed in this case.

Claims 20-21 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g., prodrugs of arabinosyl cytosine) comprising administering to an animal an acylated derivative of cytidine or deoxycytidine and an inhibitor of cytidine deaminase (e.g., tetrahydrouridine). On page 9 of the Action, it was admitted that neither Bhalla et al. nor von Borstel et al. disclose a cytidine deaminase inhibitor. In order to overcome this deficiency, the Examiner relies on Hanze et al. This rejection is respectfully traversed.

The evaluation of patentability or unpatentability under 35 U.S.C. § 103 is based on factual inquiries, one of which is the content of the prior art. As stated by the Supreme Court in *Graham v. John Deere*:

> Under § 103, the scope and content of the prior art are to be determined . . . . Against this background, the obviousness or nonobviousness of the subject matter is determined.

Graham v. John Deere Co., 383 U.S. 1, 27, 148 USPQ 459, 467 (1966)

The rejection on page 9 of the Action was based on the incorrect assertion that Hanze et al. teaches increasing free cytidine levels with an inhibitor of cytidine deaminase. It is this alleged teaching that is relied on as providing the motivation to combine the cytidine deaminase inhibitor of Hanze et al. with the acylated deoxycytidine of von Borstel et al. In this regard the rejection states:

> Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42-61) and its use to prevent the degradation of a cytidine nucleoside analog. It would have been *prima facie* obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine. One of ordinary skill would have been motivated to combine an acylated deoxycytidine and tetrahydouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinose or any other pyrimidine nucleoside analog.

Office Action mailed February 23, 2004 (page 9).

As seen from the above-quoted passage, the rejection rises and falls on whether Hanze et al. teaches that a cytidine deaminase inhibitor would result in "even higher levels of free cytidine in serum and tissue." This does not occur.

The Action does not point to any explicit teaching of Hanze et al. or other prior art in support of the position that administering an inhibitor of cytidine deaminase would

increase levels of free cytidine. Instead, the supposed expectation of increasing *in vivo* cytidine levels by administering a deoxycytidine deaminase inhibitor appears to be based on the more general assumption that inhibiting any given degradative enzyme would be expected to increase the *in vivo* levels of the substrate of that enzyme. While that assumption may be true in some cases, it is not true in others. For example, it was known that inhibiting uridine phosphorylase by administering its inhibitor 5-benzylacyclo-uridine (BAU) had no effect on plasma uridine in monkeys. This can be seen from the abstract of Davis et al. which states:

> In the monkey, BAU (30 mg/kg, i.v.) had no effect on plasma uridine despite the presence of 10-100 microM BAU levels in plasma for 1.5 hr.

Davis et al. (abstract of Biochem. Pharmacol. 45:173-181, 1993).

As seen from the above-quoted passage, administering an inhibitor of a degradative enzyme does not necessarily lead to increased plasma levels of the substrate of that enzyme. Therefore, one of ordinary skill in the art would not have had a reasonable expectation that administering an inhibitor of any given enzyme such as an inhibitor of deoxycytidine deaminase would lead to increased *in vivo* levels of the substrate of that enzyme. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). A *prima facie* case of unpatentability under 35 U.S.C. § 103 has not been made.

In regard to the evidence of unexpected results provided in the originally filed application, the Examiner has argued on page 9 of the Action that pages 42-44 of the specification contain conclusory statements about the compounds of the invention and that Example 6 does not present a result not contemplated by the prior art. The

Examiner also states that the factual evidence set forth is not commensurate with the scope of the claims, and is consistent with the Examiner's motivation theory.

In response, Example 6 provides *in vivo* evidentiary support of efficacy of the present invention. Table 13 presents the actual *in vivo* data, and clearly shows unexpected tumor regression with minimal mortality as compared to the control group. These results are unexpected and consistent with the invention as claimed. Since the results are unexpected, they could not have been "contemplated by the prior art," contrary to the Examiner's assertion. While it is true that Table 13 shows that uridine administered i.p. was marginally more effective at tumor regression as compared to TAU administered p.o., the difference in mortality rates is entirely unexpected.

Based on the above, it is clear that the various combinations of references relied upon by the Examiner do not give rise to a *prima facie* case of obviousness of any of the currently pending claims. Withdrawal of all of the outstanding obviousness rejections is accordingly respectfully requested.

Favorable reconsideration and allowance are requested.

Respectfully submitted,

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